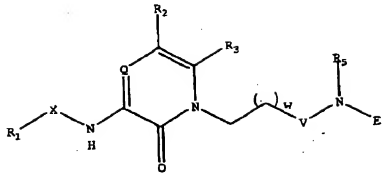


(a) X is selected from the group consisting of $-S(O_2)-$, $-N(R')-S(O)_2$, $S(O)_2-N(R')-$, $-C(=O)-$, $-OC(=O)-$, $-NHC(=O)-$, $-C(=O)N(R')-$, $-P(O)(R')-$ and a direct link, wherein R' is independently hydrogen, alkyl of 1 to 4 carbon atoms, aryl of 6 to 14 carbon atoms, aralkyl of 7 to 16 carbon atoms, with the proviso that when X is $-P(O)(R')-$, the R' is not hydrogen;

(b) R_1 is selected from the group consisting of:

(1) alkyl of 1 to 12 carbon atoms which is optionally substituted with Y_1 and/or Y_2,

(2) alkyl of 1 to 6 carbon atoms substituted with cycloalkyl of 3 to 8 carbon atoms which is optionally mono-, di-, or tri-substituted with Y_1, Y_2 and/or Y_3,

(3) cycloalkyl of 3 to 15 carbon atoms, which is optionally mono-, di-, or tri-substituted on the ring with Y_1, Y_2 and/or Y_3,

(4) heterocycloalkyl of 4 to 10 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from the group consisting of oxygen, nitrogen, and $S(O)_i$, wherein i is 0, 1 or 2, which is optionally mono-, di-, or tri-substituted on the ring with Y_1, Y_2 and/or Y_3,

(5) heterocyclo of 4 to 10 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the

heteroatoms are selected from the group consisting of oxygen, nitrogen, and $S(O)_t$, which is optionally mono-, di-, or tri-substituted on the ring carbons with Y_1, Y_2 and/or Y_3,

(6) alkenyl of 2 to 6 carbon atoms which is optionally substituted with cycloalkyl of 3 to 8 carbon atoms, which is optionally mono-, di-, or tri-substituted on the ring carbons with Y_1, Y_2 and/or Y_3,

(7) aryl of 6 to 14 carbon atoms which is optionally mono-, di- or tri-substituted with Y_1, Y_2 and/or Y_3,

(8) heteroaryl of 5 to 14 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from oxygen, nitrogen, and sulfur, and which is optionally mono-, di-, or tri-substituted with Y_1, Y_2 and/or Y_3,

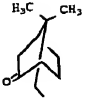
(9) aralkyl of 7 to 15 carbon atoms which is optionally substituted on the alkyl chain with hydroxy or halogen and which is optionally mono-, di-, or tri-substituted in the aryl ring with Y_1, Y_2 and/or Y_3,

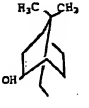
(10) heteroaralkyl of 5 to 14 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from oxygen, nitrogen, and sulfur, and which is optionally substituted on the alkyl chain with hydroxy or halogen and which is optionally mono-, di- or tri-substituted on the ring with Y_1, Y_2 and/or Y_3,

(11) aralkenyl of 8 to 16 carbon atoms which is optionally mono-, di-, or tri-substituted on the aryl ring with Y_1, Y_2 and/or Y_3,

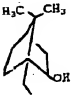
(12) heteroaralkenyl of 5 to 14 ring atoms with the ring atoms selected from carbon and heteroatoms, wherein the heteroatoms are selected from oxygen, nitrogen, and sulfur, and

which is optionally mono-, di- or tri-substituted on the ring with Y_1, Y_2 and/or Y_3,

(13) 

(14) 

(15) 

(16) 

(17) fused carbocyclic alkyl of 5 to 15 carbon atoms,

(18) difluoromethyl or perfluoroalkyl of 1 to 12 carbon atoms,

(19) perfluoroaryl of 6 to 14 carbon atoms,

(20) perfluoraralkyl of 7 to 15 carbon atoms, and

(21) hydrogen when X is a direct link;

wherein

(i) each Y_1, Y_2 and Y_3 is independently selected from the group consisting of halogen, cyano, nitro, tetrazolyl optionally substituted with alkyl of 1 to 6 carbon atoms, guanidino, amidino, methylamino, methylguanidino, $-CF_3$, $-CF_2CF_3$, $-CH(CF_3)_2$, $-C(OH)(CF_3)_2$, $-OCF_3$, $-OCF_2CF_3$, $-OCF_2H$, $-OC(O)NH_2$, $-OC(O)NHZ_1$, $-OC(O)NZ_1Z_2$, $-NHC(O)Z_1$, $-NHC(O)NH_2$, $-NHC(O)NHZ_1$, $-NHC(O)NZ_1Z_2$, $-C(O)OH$, $-C(O)OZ_1$, $-C(O)NH_2$, $-C(O)NHZ_1$, $-C(O)NZ_1Z_2$, $-P(O)_3H_2$, $-P(O)_3(Z_1)_2$, $-S(O)_3H$, $-S(O)_pZ_1$, $-Z_1$, $-OZ_1$, $-OH$, $-NH_2$, $-NHZ_1$, $-NZ_1Z_2$, N-morpholino, and $-S(O)_p(CF_2)_qCF_3$, wherein p is 0, 1 or 2, q is an integer from 0 to 5, and Z_1 and Z_2 are independently selected from the group consisting of alkyl of 1 to 12 carbon atoms, aryl of 6 to 14 carbon atoms, heteroaryl of 5 to 14 atoms having 1 to 9 carbon atoms, aralkyl of 7 to 15 carbon atoms, and heteroaralkyl of 5 to 14 ring atoms, or

(ii) Y_1 and Y_2 are selected together to be $-O[C(Z_3)(Z_4)]_rO-$ or $-O[C(Z_3)(Z_4)]_{r+1}-$, wherein r is an integer from 1 to 4 and Z_3 and Z_4 are independently selected from the group consisting of hydrogen, alkyl or 1 to 12 carbon atoms, aryl of 6 to 14 carbon atoms, heteroaryl of 5 to 14 ring atoms having 1 to 9 carbon atoms, aralkyl of 7 to 15 carbon atoms, and heteroaralkyl of 5 to 14 ring atoms;

(c) Q is $-C(R_4)-$;

(d) R_2 is selected from the group consisting of hydrogen, halogen and alkyl of 1 to 6 carbon atoms;

(e) R_3 is selected from the group consisting of hydrogen, alkyl 1 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, alkoxy of 1 to 6 carbon atoms, halogen, and trifluoromethyl;

(f) alternatively, R_2 and R_3 are selected together and are $-(CH_2)_k-$ where k is 3 or 4;

(g) R_4 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms, hydroxy, alkoxy of 1 to 8 carbon atoms, aralkyl of 7 to 15 carbon atoms, alkyl of 1 to 5 carbon atoms substituted with cycloalkyl of 3 to 8 carbon atoms, $-NHR_8$, $-S(O)_tR_8$ and $-C(=O)R_8$ where t is 0, 1 or 2;

(h) w is 0, 1 or 2;

(i) V is $-CH(R_9)-$;

(j) R_5 is hydrogen or alkyl of 1 to 6 carbon atoms;

(k) E is heteroaryl of 6 to 10 ring atoms having from 1 to 4 ring nitrogen atoms and the remainder of the ring atoms carbon atoms and which is substituted with R_6 and R_7;

(l) R_6 and R_7 are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkyl of 1 to 4 carbon atoms substituted with alkoxy of 1 to 4 carbon atoms, trifluoromethyl, $-C(=O)OR_{10}$, $-NHR_{10}$, $-C(=O)R_{10}$, $-C(=O)NHR_{10}$, $-OC(=O)NHR_{10}$, $-C(=NR_{10})NHR_{11}$, and $-N(R_{12})-C(=NR_{10})NHR_{11}$; and

(m) R_8, R_9, R_{10}, R_{11} and R_{12} are independently selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms and $-(CF_2)_jCF_3$ wherein j is 0, 1, 2 or 3; or pharmaceutically acceptable salts thereof.

2. (Cancelled)

2
3. (Previously presented) A compound according to claim 1 wherein R_9 is hydrogen.

3
4. (Original) A compound according to claim 3 wherein X is $-S(O)_2-$ or a direct link.

4
5. (Original) A compound according to claim 4 wherein R_1 is substituted or unsubstituted aralkyl.

5
6. (Original) A compound according to claim 5 wherein E is

6
7. (Original) A compound according to claim 6 wherein R_6 and R_7 are independently hydrogen or halogen.

7
8. (Original) A compound according to claim 7 wherein at least one of R_6 and R_7 is hydrogen.

9. (Cancelled)

8
10. (Previously presented) A compound according to claim 8 wherein w is 1.

9
11. (Previously presented) A compound according to claim 8 wherein R_4 is hydrogen.

10
12. (Original) A compound according to claim 11 wherein w is 1.

13. (Cancelled)

11
14. (Previously presented) A compound according to claim 1 wherein X is $-S(O)_2-$.

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12
15. (Original) A compound according to claim 14 wherein R_9 is hydrogen or methyl.

13
16. (Cancelled)

17. (Cancelled)

13
18. (Previously presented) A compound according to claim 15 wherein R_1 is substituted or unsubstituted aralkyl.

14
19. (Original) A compound according to claim 18 wherein R_3 is hydrogen.

15
20. (Original) A compound according to claim 19 wherein w is 0 or 1.

16
21. (Original) A compound according to claim 1 wherein E is

17
22. (Original) A compound according to claim 21 wherein R_6 and R_7 are independently hydrogen or halogen.

18
23. (Original) A compound according to claim 22 wherein at least one of R_6 and R_7 is hydrogen.

24. (Cancelled)

19
25. (Previously presented) A compound according to claim 23 wherein R_9 is hydrogen or methyl.

20
26. (Previously presented) A compound according to claim 1 wherein X is $-S(O_2)-$ or a direct link.

21
27. (Original) A compound according to claim 26 wherein R_1 is unsubstituted aralkyl, substituted aralkyl or alkyl substituted with cycloalkyl in which the cycloalkyl group is substituted with aryl or heteroaryl.

22
28. (Original) A compound according to claim 27 wherein R_2 is hydrogen and R_3 is hydrogen or methyl.

23
29. (Original) A compound according to claim 28 wherein R_3 is methyl.

Claims 30 to 32 (Cancelled)

24
33. (Previously presented) A compound according to claim 1 selected from the group consisting of Compounds A, E, F, G, H, I, J, K, L, M, N, P, Q and R depicted in Figures 1A and 1B.

25
34. (Currently amended) A pharmaceutical composition ~~for treating or decreasing the incidence of a condition in a mammal characterized by abnormal thrombosis,~~ comprising a ~~therapeutically~~ pharmaceutically acceptable carrier, and a therapeutically effective amount of compound of claim 1.

26
35. (Currently amended) A pharmaceutical composition ~~for treating or decreasing the incidence of a condition in a mammal characterized by abnormal thrombosis,~~ comprising a ~~therapeutically~~ pharmaceutically acceptable carrier, and a therapeutically effective amount of compound of claim 3.

27
36. (Currently amended) A pharmaceutical composition ~~for treating or decreasing the incidence of a condition in a mammal characterized by abnormal thrombosis,~~ comprising a ~~therapeutically~~ pharmaceutically acceptable carrier, and a therapeutically effective amount of compound of claim 6.

28

~~37.~~ (Currently amended) A pharmaceutical composition ~~for treating or decreasing the incidence of a condition in a mammal characterized by abnormal thrombosis,~~ comprising a ~~therapeutically~~ pharmaceutically acceptable carrier, and a therapeutically effective amount of compound of claim 15.

29

~~38.~~ (Currently amended) A pharmaceutical composition ~~for treating or decreasing the incidence of a condition in a mammal characterized by abnormal thrombosis,~~ comprising a ~~therapeutically~~ pharmaceutically acceptable carrier, and a therapeutically effective amount of compound of claim 19.

~~39.~~ (~~Amended~~) (Currently amended) A pharmaceutical composition ~~for treating or decreasing the incidence of a condition in a mammal characterized by abnormal thrombosis,~~ comprising a ~~therapeutically~~ pharmaceutically acceptable carrier, and a therapeutically effective amount of compound of claim 53.

~~40.~~ (~~Amended~~) (Currently amended) A pharmaceutical composition ~~for treating or decreasing the incidence of a condition in a mammal characterized by abnormal thrombosis,~~ comprising a ~~therapeutically~~ pharmaceutically acceptable carrier, and a therapeutically effective amount of compound of claim 55.

30

~~41.~~ (Currently amended) A pharmaceutical composition ~~for treating or decreasing the incidence of a condition in a mammal characterized by abnormal thrombosis,~~ comprising a ~~therapeutically~~ pharmaceutically acceptable carrier, and a therapeutically effective amount of compound of claim 33.

31
42. (Currently amended) A method for treating ~~or decreasing the incidence of~~ a condition in a mammal characterized by ~~abnormal~~ thrombosis, comprising administering to said mammal a therapeutically effective amount of the compound of claim 1.

32
43. (Currently amended) A method for treating ~~or decreasing the incidence of~~ a condition in a mammal characterized by ~~abnormal~~ thrombosis, comprising administering to said mammal a therapeutically effective amount of the compound of claim 3.

33
44. (Currently amended) A method for treating ~~or decreasing the incidence of~~ a condition in a mammal characterized by ~~abnormal~~ thrombosis, comprising administering to said mammal a therapeutically effective amount of the compound of claim 6.

34
45. (Currently amended) A method for treating ~~or decreasing the incidence of~~ a condition in a mammal characterized by ~~abnormal~~ thrombosis, comprising administering to said mammal a therapeutically effective amount of the compound of claim 15.

35
46. (Currently amended) A method for treating ~~or decreasing the incidence of~~ a condition in a mammal characterized by ~~abnormal~~ thrombosis, comprising administering to said mammal a therapeutically effective amount of the compound of claim 19.

48
47. (~~Amended~~) (Currently amended) A method for treating ~~or decreasing the incidence of~~ a condition in a mammal characterized by ~~abnormal~~ thrombosis, comprising administering

to said mammal a therapeutically effective amount of the compound of claim ~~53~~ 40.

49
~~48~~. (Currently amended) A method for treating ~~or decreasing the incidence of~~ a condition in a mammal characterized by ~~abnormal~~ thrombosis, comprising administering to said mammal a therapeutically effective amount of the compound of claim ~~55~~ 47.

36
~~48~~. (Currently amended) A method for treating ~~or decreasing the incidence of~~ a condition in a mammal characterized by ~~abnormal~~ thrombosis, comprising administering to said mammal a therapeutically effective amount of the compound of claim 33.

37
~~50~~. (Previously presented) A compound according to claim 15 wherein R_4 is hydrogen.

38
~~51~~. (Previously presented) A compound according to claim 37 ~~50~~ wherein R_2 is hydrogen.

39
~~52~~. (Previously presented) A compound according to claim 38 ~~51~~ wherein R_3 is methyl.

40
~~53~~. (Previously presented) A compound according to claim 29 wherein R_4 is hydrogen.

41
~~54~~. (Previously presented) A compound according to claim 1 wherein R_4 is hydrogen.

42
~~55~~. (Previously presented) A compound according to claim 41 ~~54~~ wherein R_2 is hydrogen.

43
~~56~~. (Previously presented) A compound according to claim 42 ~~55~~ wherein R_3 is methyl.

44

57. (Previously presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of any of claims 1, 3, 6, 15, 19, 33, 53 or 55.

40 42

45

58. (Currently amended) A method of ~~preventing or~~ treating in a mammal a condition of ~~abnormal~~ thrombus formation which comprises administering to said mammal a therapeutically effective amount of a compound of any of claims 1, 3, 6, 15, 19, 33, 53 or 55.

40 42

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Appln. No. 09/905,644 (series code ↑ ↑ serial no.)
Filed: July 13, 2001
TITLE: NOVEL NON-COVALENT THROMBIN INHIBITORS

Group Art Unit: 1624
Examiner: Balasubramanian, V.
Atty. Dkt. PM 018813-0272492 (M#)
Date: December 23, 2003

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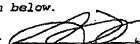
Name Suzanne L. Biggs Sig.  Date December 23, 2003

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